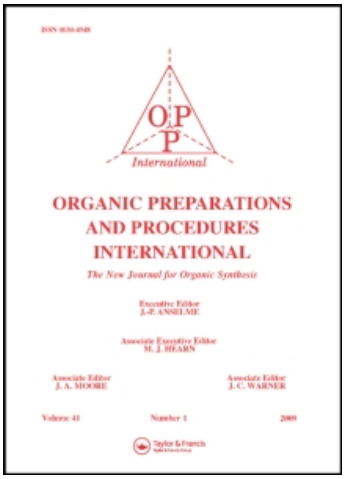

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IMPROVED SYNTHESIS OF 3,4-DIHYDRO-2,6-DIMETHYL-4-OXOQUINAZOLINE

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OPPI BRIEFS

IMPROVED SYNTHESIS OF 3,4-DIHYDRO -2,6-DIMETHYL-4-OXOQUINAZOLINE

Submitted by Shiyan Chen, Jimao Lin* and Bingjie Qin
(03/11/01)

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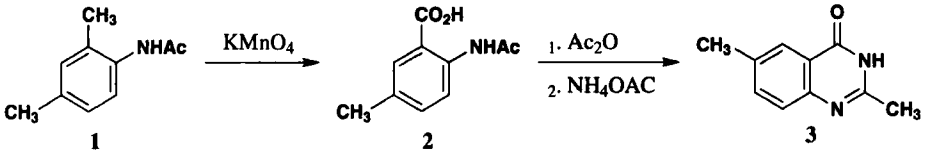
3,4-Dihydro-2,6-dimethyl-4-oxoquinazoline(**3**), a key intermediate in the synthesis of a number of potent thymidylate synthase (TS) inhibitor,[1-4] has been prepared[6,7] by reaction of 2-acetamido-5-methylbenzoic acid (**2**) with acetic acid anhydride and ammonium acetate. However, in these syntheses **2** was obtained by acetylation of expensive 2-amino-5-methylbenzoic acid. We now describe the preparation of **2** from cheaper 2,4-dimethylacetanilide (**1**)[5] and also report a procedure for the synthesis of **3** (in 20% overall yield from **1**) by the direct use of the mixture of oxidation products of **1**, containing 2-acetamido-5-methylbenzoic acid (**2**), 4-acetamido-3-methylbenzoic acid and 4-acetamidoisophthalic acid.



1 2 3

It has been reported that *N*-acetylated xylidines could be oxidized to the corresponding carboxylic acid derivatives by potassium permanganate in neutral aqueous solution.[5] However, the oxidation of 2,4-dimethylacetanilide (**1**) with a 4:1 molar ratio of potassium permanganate only gave 4-acetamidoisophthalic acid. In our procedure, the potassium permanganate was added in four separate times at 80°C (molar ratio in each case was 1:1) as described in the Experimental Section to give **2** in 23% yield from **1**.

EXPERIMENTAL SECTION

^{1}H NMR was recorded at 90 MHz nuclear magnetic resonance spectrometer in $CDCl_3$ solvent or in DMSO-d_6 solvent (TMS as internal standard). Chemical shifts are reported in δ units (ppm). Mps. were determined on a X-4 melting point apparatus.

2-Acetamido-5-methylbenzoic Acid (2).- A mixture of 2,4-dimethylacetanilide[8] (8.15 g, 0.05 mol) and water (300 mL) was heated to 80°C. Potassium permanganate (7.9 g, 0.05 mol) was added over a period of eight minutes to the hot mixture. When the purple color of potassium permanganate had disappeared, the mixture was filtered. The filter cake (**A**) which contains unreacted **1** was collected. The filtrate was extracted with 3 x 200 mL ethyl ether, and then ether was distilled from the extract to give unchanged 2,4-dimethylacetanilide (**1**) which was combined with the filter cake **A** and used in the next oxidation. The aqueous layer (**B**) was acidified to pH 2-3 with conc. hydrochloric acid (*see later*).

The filter cake (**A**) and unchanged 2,4-dimethylacetanilide (**1**) in water (300mL) were heated to 80°C and treated as above with potassium permanganate (7.9 g, 0.05 mol). This process was carried out two more times (for a total of four), to give unreacted 2,4-dimethylacetanilide (1.50 g, 18%) recovered by extraction of the aqueous layer with ether and of the filter cake (MnO_2) with ethanol, thus indicating an 82% consumption of 2,4-dimethylacetanilide. Collection and washing (with cold water) of the precipitates obtained by cooling the acidified aqueous layers (**B**) of each oxidation to 0°C gave, after drying, 6.05 g of a mixture of compound **2**, 2,4-acetamido-3-methybenzoic acid and 4-acetamidoisophthalic acid. Their R_f (TCL: silica gel, 25% v/v dichloromethane in ethyl acetate) are 0.50, 0.25, 0.05 respectively. The crude mixture of products was separated by chromatography using a 25% v/v dichloromethane in ethyl acetate as eluent to give 1.80 g (23%) of **2**, mp.178-180°C, *lit.*[9a] 179°C, 2.64 g (34%) of 4-acetamido-3-methylbenzoic acid, mp.114-116°C, *lit.*[9a] 115°C, and 1.56 g (17%), mp. 294-296°C (dec.), *lit.*[9b] 295-296°C (dec.) of 4-acetamidoisophthalic acid.

^{1}H NMR($CDCl_3$) of **2**: δ 2.25 (s, 3H, -$COCH_3$), 2.35 (s, 3H, =C-CH_3), 5.20 (br, 1H, -NH), 7.40 (dd, 1H,ArH), 7.90 (d, 1H, ArH), 8.60 (d, 1H, ArH), 10.79 (s, 1H, -CO_2H).

3,4-Dihydro-2,6-dimethyl-4-oxoquinazoline (3).- A portion of the crude mixture (3.86 g) of the oxidized products obtained above, acetic acid anhydride (4.07 g, 0.04 mol) and petroleum ether (60-90°C) (13.8 mL) were heated to reflux for about 3 hrs and cooled to 20-40°C and ammonium acetate (6.9 g, 0.09 mol) was added. The mixture was distilled under atmospheric pressure until approximately 8 mL of petroleum ether (60-90°C) had distilled. Acetic acid (20 mL) was then added and the distillation was continued until approximately another 15 mL of distillate was collected and the mixture was heated at reflux for 16 hrs. After cooling to room temperature, water (11 mL) was added and the mixture was then cooled to 4-6°C and stirred for 2 hrs. The resulting mixture was filtered to collect crude product and the pH of the filtrate was brought to 9 with solid sodium hydroxide. The solid which precipitated was collected and the filtrate was extracted with ethyl ether and the solvent was evaporated to give additional solid. The combined crude solids were recrystallized from ethanol to give 0.92 g (20%, calculated from 2,4-dimethylacetanilide) of **3**, mp. 249-251°C. ^{1}H NMR ($CDCl_3$): δ 2.49 (s, 3H, -CH=C-CH_3), 2.56 (s, 3H, -N=C-CH_3), 6.80 (1H, br, -NH), 7.57 (s br., 2H, quinazoline 7-H, 8-H), 8.06(s, 1H, quinazoline 5-H).

Anal. Calcd for $C_{10}H_{10}N_2O$: C, 68.95; H, 5.79; N, 16.08. Found: C, 68.98; H, 5.76; N, 15.96

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PREPARATION OF 3-BROMO-2-(NITROMETHYLENE)PYRROLIDINE AND 3-BROMO-*N*-METHYL-1-NITRO-1-BUTEN-2-AMINE

Submitted by J. Geno Samaritoni
(03/16/04)

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Since its discovery in the early 1970s, the nitromethylene class of insect control agents has received considerable attention within the agrochemical industry.[1] Recently we had occasion to investigate a series of compounds (**1**)[2] featuring the nitromethylene group in three slightly varied environments (*Fig. 1*). Our approach required the syntheses of the allylic bromides **2a-c**. Since the preparation of **2c** is described in the literature,[3] the same strategy was applied to the